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Gene Section

Review

DND1 (DND microRNA-mediated repression inhibitor 1)

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Abstract

DND1 is a RNA binding protein. Initially identified in the zebrafish, where knockdown of dnd in the early embryo resulted in loss of primordial germ cells (Weidinger et al., 2003). Mutations in Dnd1 in mice and rats, thought to result in expression of a truncated DND1 protein, are oncogenic and result in germ cell depletion as well as germ cell tumors (Youngren et al., 2005; Northrup et al., 2012). DND1 is required for the survival of primordial germ cells during early development. Primordial germ cells are the stem cells from which germ cell tumors arise (Stevens, 1967). Total deficiency of DND1 in mice results in early embryonic lethality (Zechel et al., 2013). In humans, mutations and deregulation of DND1 expression have been reported in testicular cancer as well as other types of cancers (Bhandari et al., 2012; Linger et al., 2008; Liu et al., 2010; Sijmons et al., 2010). One function of DND1 is as a translational regulator (Kedde et al., 2007).

Keywords

translation regulation, miRNA, germ cell, germ cell tumor, DND1

Identity

Other names: MGC34750; RBMS4

HGNC (Hugo): DND1

Location: 5q31.3, located between bases 140,670,794-140,673,586 on the reverse strand of human Chr 5 (Ensembl).

Local order: Flanking DND1 on the 5' end is WDR55 (WD repeat domain 55) located on the forward strand, followed by DND1 (on reverse strand) and at the 3'-end, HARS (histidyl-tRNA synthetase) (on the reverse strand).

DNA/RNA

Transcription

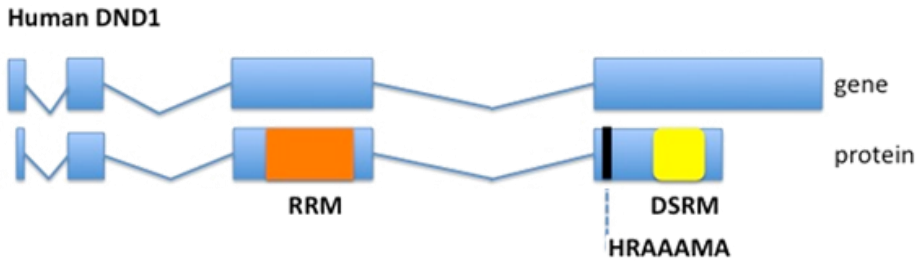
Unlike human DND1, mouse Dnd1 encodes two alternate spliced transcripts that differ at the N-terminus and which give rise to α and β-isoforms of DND1. DND1-α is expressed in early embryos and DND1-β in the germ cells of adult testis (Bhattacharya et al., 2007).

Protein

Description

DND1 contains a RNA recognition motif (RRM) through which it interacts with mRNA (Northrup et al., 2012; Weidinger et al., 2003; Youngren et al., 2005).

It also has a double strand RNA binding domain (DSRM) at the C-terminus end, the function of which has not been evaluated. DND1 has sequence similarity with A1cf, which is a RNA binding subunit of the Apobec1 cytidine deaminase that edits specific sites in specific mRNAs (Youngren et al., 2005). A conserved HRAAAMA motif is found in DND1 and in A1cf (Zechel et al., 2013) and the ATPase activity of zebrafish Dnd is ascribed to this motif (Liu and Collodi, 2010).



Human DND1 has 1 transcript (1605 bp) encoding a protein of 353 aa. Human DND1 has a RNA recognition motif (RRM), double strand RNA binding domain (DSRM), and the HRAAAMA motif (that is also found in mouse and rat DND1).

Expression

Expressed in embryonic and adult germ cells, the gonads and in testicular germ cell tumors (Bhattacharya et al., 2007; Northrup et al., 2012; Weidinger et al., 2003; Youngren et al., 2005). Also expressed in other cell types such as skin and pancreas (Basu et al., 2011; Bhandari et al., 2012). Is expressed in the early embryo of Xenopus (Bauermeister et al., 2015; Mei et al., 2013).

Localisation

ND1 localizes to the cytoplasm in perinuclear sites as well as in the nucleus of some cell types (Bhattacharya et al., 2008; Bhattacharya et al., 2007; Mickoleit et al., 2011; Slanchev et al., 2009). In the cytoplasm of male embryonic germ cells, DND1 co-localizes with NANOS2 in P-bodies (Suzuki et al., 2015).

The Xenopus Dnd protein has a germplasm localization signal and nuclear localization signal. In the fertilized embryo, Dnd moves from the cortex to the perinuclear region with germplasm and enters the nucleus. It is speculated that Dnd carries RNA into the nucleus to trigger germline specification (Taguchi et al., 2014).

Function

DND1 is implicated in different aspects of translation regulation that impact embryonic and primordial germ cell development and cancer. The molecular function of DND1 has been delineated from studies in rodents, zebrafish and Xenopus.

(a) DND1 binds to the 3'-UTR (untranslated region) of mRNAs to displace miRNA interaction with specific mRNAs (Kedde et al., 2007; Liu et al., 2010). For example, DND1 blocks access of specific miRNAs to their 3' target in CDKN1B (P27) and LATS2 mRNA. Human and mouse DND1 interacts with mRNAs that encode pluripotency factors (POU5F1 (OCT4), SOX2 , NANOG, LIN28), regulators of cell cycle (LATS2, TP53, p21 and p27) and apoptotic factors (BCL2L1 (BCLX) andBAX) (Cook et al., 2011; Zhu et al., 2011).

Zebrafish DND1 blocks miR-430 from huB, Nanos and TDRD7 3'-UTR and also regulates translation of geminin mRNA through binding to its 3? -UTR (Chen et al., 2010; Kedde et al., 2007; Mickoleit et al., 2011).

(b) DND1 interacts with apolipoprotein B editing complex 3 (APOBEC3) (Bhattacharya et al., 2008). Human APOBEC3G inhibits DND1 function. APOBEC3G blocks DND1 function to restore the translational inhibitory effect of miRNAs on the 3'-UTR of P27, LATS2 and GJA1 (CX43) (Ali et al., 2013).

Mouse c-JUN interacts with DND1 and co-localizes to the nuclei. DND1 and c-JUN caused increased transcriptional activity of activator protein 1 (Zhang et al., 2015).

(c) Mouse DND1 directly interacts with NANOS2 to load specific mRNAs into the CCR4-NOT (CNOT) deadenylase complex (Suzuki et al., 2015). This results in translational suppression of specific RNAs that are required during germ cell development and thus conditional deletion of DND1 disrupts male germ cell differentiation.

(d) Zebrafish DND1 protein possesses Mg(2+)-dependent ATPase activity that is required for primordial germ cell viability and formation. The ATPase region is mapped to the C terminus of DND1 (Liu and Collodi, 2010).

(e) DND1 transports mRNA transcripts from germ cell nuclei to germ cell granules (Slanchev et al., 2009).

(f) Deletion of DND1 in mice indicates it is essential for embryonic viability (Zechel et al., 2013). Repression or ablation of Dnd In Xenopus and zebrafish embryos results in loss of primordial germ cells and their failure to migrate into the developing gonads (Horvay et al., 2006; Weidinger et al., 2003).

(g) In the early embryo of Xenopus, Dnd is required to regionally anchor key regulators of the vegetal cortical microtubule assembly for axis specification. Dnd binds to 3'-UTR of trim36, an E3 ubiquitin ligase, which is essential for microtubule assembly. The microtubules translocate dorsal determinants. Lack of Dnd causes ventralization of frog embryos (Mei et al., 2013).

In turn, Xenopus Dnd mRNA is localized vegetally to the RNP complex by Celf, a component of the vegetal localization RNP complex (Bauermeister et al., 2015). Celf interacts with the late element (LE)

of Dnd RNA. LE of Dnd mRNA also interacts with Elavl1 and Elav2 (Arthur et al., 2009).

Implicated in

Germ cell tumors including Testicular Germ Cell Tumors (TGCTs or testicular cancer) and Ovarian germ cell tumors (OGCTs)

The 5q31.3 region encompassing DND1 is frequently deleted in male TGCTs (al-Jehani et al., 1995; Faulkner et al., 2000; Peng et al., 1999). Two studies detected DND1 mutations upon sequencing the exons of DND1 in patients with TGCTs (Linger et al., 2008 ; Sijmons et al., 2010) although mutations in DND1 appear to be rare in human TGCTs.
In one study, DNA from 263 familial and sporadic TGCT patients were sequenced. A possible pathogenic missense mutation in exon 3 (c.A301C, p.Glu86Ala) was identified in one patient. This mutation resides within the functional, evolutionary conserved RNA recognition motif (Linger et al., 2008).
In another study, sequencing exons 1 to 4 of DND1 from peripheral blood lymphocytes in 272 men, with both sporadic and familial TGCT, detected one non familial mutation (c.C657G, p.Asp219Glu) in exon 4. The wild-type DND1 was not lost in the patient (Sijmons et al., 2010).
Analysis of the human DND promoter revealed 15 CpG sites. However, no significant differences in CpG methylation levels have been observed in DNA from blood of patients with TGCT cases compared to controls (Mirabello et al., 2012).

Oncogenesis

The function DND1 in TGCT oncogenesis has been gleaned from studies in rodent models.
The Ter mutation is a single base substitution in exon 3 of Dnd1 that transforms an arginine residue to a premature stop codon (p.Arg178X) (Youngren et al., 2005). In the 129 mouse, the Ter mutation (in DND1) has been characterized as a modifier gene for amplifying the incidence of spontaneous TGCTs (Asada et al., 1994; Noguchi and Stevens, 1982). The 129-Ter mouse is a model for prepubertal type I testicular germ cell tumors (Oosterhuis and Looijenga, 2005). Neoplastic transformation of germ cells and tumorigenesis takes place during embryogenesis (Noguchi and Noguchi, 1985; Stevens, 1967). The germ cells in Ter male mice fail to enter mitotic arrest in G0 (Cook et al., 2011)
A complete loss-of-function of DND1 leads to early embryonic lethality. However, the loss-of-function Dnd1 allele does not cause TGCT (Zechel et al., 2013).
In Ter-WKY/Ztm rats, a point mutation in exon 4 of rat Dnd1 introduces a premature stop codon that likely results in expression of a C-terminus truncated DND1 protein. This results in congenital ovarian germ cell tumors (OGCTs) in females and TGCTs in males (Northrup et al., 2012). Thus DND1/Ter acts as a tumor suppressor in the rat.
Germ cells derived from rat Ter embryos are more easily transformed into pluripotent cells in culture compared to their wild type counterparts (Northrup et al., 2011).

Skin tumorigenesis

RAS transformed human HaCaT cells show reduced expression of DND1, loss of DND1 mRNA and protein (Bhandari et al., 2012). In this cell type, DND1 blocks miR-21 from the 3'-UTR of the mRNA of the DNA repair gene MSH2. Thus, lower DND1 levels in RAS transformed HaCaT cells results in decreased MSH2 levels in the cell.

Human tongue squamous cell carcinoma (TSCC)

Human tongue squamous cell carcinoma (TSCC) cells and tumors up-regulate miR-24. In turn, miR-24 interacts with the 3'-UTR of DND1 mRNA to reduce expression of DND1. Thus miR-24-mediated decrease in DND1 expression leads to decreased cyclin-dependent kinase inhibitor 1B (CDKN1B/ P27) expression and enhanced proliferation and reduced apoptosis in TSCC cells (Liu et al., 2010).

Colon tumorigenesis

The truncated DND1 mutant (Ter) significantly increases polyp number and burden in the Apc+/Min model of intestinal polyposis (Zechel et al., 2013).

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